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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,517	02/02/2001	Gregory Grabowski		1629

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/775,517	GRABOWSKI ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-4,10-22,28-36 and 66-68*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *1/28/04*.

10. ☒ Other: *892 attached*

Jon P Weber, Ph.D.
Primary Examiner
Art Unit: 1651

Status of the Claims

The response with amendments and Hui Declaration filed 28 January 2004 has been received and entered. Claims 1-4, 10-22, 28-36 and 66-68 have been presented for examination.

Information Disclosure Statement

The information disclosure statement filed 28 January 2004 fails to comply with 37 CFR 1.97(d) because it lacks a statement as specified in 37 CFR 1.97(e). It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

Claims 1-4, 10-22, 28-36 and 66-68 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993) and Walters et al. (1994) in view of Coates et al. (1986).

It is argued that all of the cited references use secondary agents to induce increased LAL not direct addition of LAL as claimed. It is urged that the argument in the Office action that the limited ways one could increase LAL: 1) induction, 2) gene therapy, and 3) direct addition is only "obvious to try" which is not the standard under 103. It is urged that the examples suggested of streptokinase and TPA are targeted therapy for discrete events whereas the instant therapy is likely to be used for months or years. Several references are provided: Rademacher et al. (1989), Updike (1972), and Desnick et al. (2002) that discuss the problems with enzyme replacement therapy and are urged to provide evidence away from direct enzyme addition. It is argued that Escary et al. (1999), as discussed by Hui declaration, teaches away from the instant invention

because HSL overexpression leads to greater susceptibility to atherosclerosis – a paradoxical effect. Finally, it is argued that Haemmerle et al. (2003) teaches away from using HSL gene or protein to treat atherosclerosis.

The obvious to try proscription arises when there is 1) no reasonable likelihood of success or 2) when there is not a discrete set of options available. In the instant case there are only three logically possible options, clearly discrete. As argued in the Office action, induction is what the references show, gene therapy is still too undeveloped to be expected to be useful. However, there is much experience with direct enzyme therapy, albeit with other enzymes. Specific well known non-limiting examples were provided by way of illustration. That these are used for specific events is not probative. There is much success with these and many other exogenous enzyme therapies. There are a large number of enzymes that have been added for therapy. Much success has been had with various hydrolases in a number of different treatments e.g., digestive enzymes, scar removal, cataract treatments, etc. These particular examples were chosen because of their action in a similar intra-arterial milieu as the instant LAL. Hence, there is a reasonable likelihood of success for addition of exogenous enzyme. The obvious to try issue does not arise.

Officially the references have not been considered as other than evidence (*vide supra*). However, it is important to note that Rademacher et al. (1989), Updike (1972), and Desnick et al. (2002) are all referring to enzyme replacement therapy when there is a genetic deficiency in a particular enzyme. The problems in replacement therapy are of no matter when one is considering an enzyme-based therapy. The issues of cell uptake, clearance, targeting, immunological compatibility, etc. mentioned in these articles do not arise, especially in the

context of an enzyme therapy that takes place within the lumen of the arteries and veins. Enzyme replacement therapy is necessarily a life-long commitment; else the deficiency will not be remedied. Two of these references are quite old and of dubious value to the technology current at the time the alleged invention was made. The considerations with the use of streptokinase and TPA, which are used in enzyme therapy as opposed to enzyme replacement therapy, are considerably different. As long as human enzyme is used, it will not be expected to cause immunological problems. Human enzyme, free of viral particles, is readily available by recombinant means. As discussed in Tietge et al. (2001), human LAL cDNA has been available since 1997. Accordingly, these alleged issues are not well taken.

Finally, the question arises whether Escary (1999) as argued by the Hui Declaration and Haemmerle et al. (2003) teach away from HSL induction of LAL to treat atherosclerosis. First, HSL induction of LAL is not the only induction method relied upon. Assuming *in arguendo* that Hui's declaration and Haemmerle et al. do teach away from using HSL to induce LAL for treatment of atherosclerosis, the rejection is not invalidated because other methods to induce LAL are provided.

Hui argues that Escary et al. attributes the increased lesion formation to decreased HDL upon feeding them an athergenic diet. Escary et al. has been thoroughly reviewed; but the basis for this assertion cannot be found. Escary et al. report at page 403 that the HSL overexpressing transgenic mice 1) have increased cholesteryl-ester hydrolysis and 2) have increased atherosclerotic lesions compared to control mice. Escary et al. instead state that the increased hydrolysis rate leads to increased free cholesterol levels and subsequent increased re-esterification and increased atherosclerosis. Escary et al. go on to state that ACAT is stimulated

by free cholesterol. Further, they indicate that their studies with RAW cells and HSL overexpression showed increased ACAT activity. Hence, Escary et al. conclude that their results are consistent with the interpretation that in the transgenic mice, ACAT activity is higher than nCEH activity. Thus, increasing nCEH activity by HSL overexpression leads to even higher ACAT activity, thereby increasing atheroscleros susceptibility.They conclude that simply increasing nCEH activity without accounting for ACAT activity may not be sufficient to protect from atherosclerosis. Hui may be an expert, but the opinion in the Declaration is not consistent with what Escary et al. actually say. It is not clear what the paradoxical effect seen in Escary et al. (1999) means with respect to LAL. Nevertheless, Escary et al. (1999) will be taken as evidence that increasing HSL by overexpression, which leads to increased neutral cholesterol ester hydrolase (aka, LAL) activity in macrophage foam cells, does not lead to decreased susceptibility to atherosclerosis, but its opposite. Accordingly, Escary et al. (1998) is withdrawn from this rejection.

Applicant's arguments filed 28 January 2004 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 103 is adhered to for the reasons of record and the additional reasons above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 571-272-0925. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
19 February 2004